REMARKS

Upon entry of the present amendment, claims 54-63 and 65-103 will be pending in the application. In the present amendment, claims 64 and 104 are canceled without prejudice. Claims 54 and 100 are amended to specify that the less soluble substance is a lipid and the more soluble substance is a surfactant or more soluble form of the lipid. Claim 60 is amended to remove the reference to analogs and derivatives. Claim 66 is amended to remove the reference to a surfactant-like molecule. Claim 81 is amended to remove the reference to practically sufficient transport rate across a barrier. No new matter has been introduced by these amendments. Support is found throughout the specification, for example, at page 26, last paragraph (claims 54 and 100).

In the present amendment to the specification, the paragraph bridging pages 27-28 is amended to remove the reference to Span™ or Arlacel™ and correct a typographical error. No new matter is added by this amendment, which simply removes an exemplary parenthetical and makes an obvious correction. The third paragraph on page 14 is amended to remove the term "etc." No new matter is added by this amendment, which simply removes an additional term.

Entry of this amendment is respectfully requested.

I. Interview Summary

Applicants respectfully thank Examiners Hissong and Landsman for the courtesy of a telephone interview with the undersigned and Dr. Ann-Louise Kerner on May 3, 2007 to discuss the outstanding enablement and prior art rejections. The Examiners indicated that an amendment as presented herein amending the independent claims to specify a lipid and a surfactant (or more soluble form of the lipid) should be helpful in overcoming the enablement rejection. The Examiners also agreed that an inventor declaration as submitted herewith, demonstrating the non-obviousness and unexpected nature of the claimed subject matter, would be helpful in overcoming the § 103 rejection.

II. Specification

The Office Action objects to the use of the trademarks Span™, Arlacel™ and Transfersulin™ in the specification.

Without acquiescing in the propriety of this objection, in order to expedite prosecution, the present amendment has removed the reference to Arlacel™ and Span™ at page 27, last line of the specification, thus rendering moot the objection to these terms. Because the reference to these trademarked materials was merely an exemplary parenthetical, removal of this language neither introduces new matter nor reduces the scope of coverage of the description.

Regarding the term Transfersulin™, described at page 41 of the specification as a suspension of carriers loaded with insulin, the Office Action asserts that the specification does not make clear what the carriers are. Applicants respectfully disagree. Transfersulin™ refers to an insulin-loaded transfersome, *i.e.*, a lipid carrier carrying a specified amount of insulin. The use of the specific Transfersulin™ compositions identified at page 41 of the specification, including lipid composition and insulin concentration, is clearly described in the Examples section at pages 40-44 of the specification and corresponding figures, including Examples 1 and 2, and Figure 1. Accordingly, Applicants respectfully submit that the objection to the term Transfersulin™ should be reconsidered and withdrawn.

III. Claim Rejections Under 35 U.S.C. § 112, 1st Paragraph – Enablement

Claims 54-104 were rejected under § 112, first paragraph, as lacking enablement because the specification allegedly does not provide sufficient supporting disclosure for penetrants containing substances other than a surfactant and a lipid.

Without acquiescing in the propriety of the rejection, in order to expedite prosecution, independent claims 54 and 100 have been amended herein to recite "wherein the less soluble substance is a lipid and the more soluble substance is a surfactant or more soluble form of the lipid," and independent claim 104 has been canceled. As acknowledged in the Office Action, the specification provides guidance regarding the preparation of penetrants including lipids and surfactants. Accordingly, Applicants respectfully submit that the present amendment obviates this enablement rejection, which should thus be reconsidered and withdrawn.

IV. Claim Rejections Under 35 U.S.C. § 112, 1st Paragraph – Written Description

Claim 60 was rejected under § 112, first paragraph, because the specification allegedly does not provide sufficient written description for analogs and derivatives of anti-cytokine antibodies.

Without acquiescing in the propriety of the rejection, in order to expedite prosecution, claim 60 has been amended herein to remove the reference to analogs and derivatives. Thus, the present written description rejection is moot and should be reconsidered and withdrawn.

V. Claim Rejections Under 35 U.S.C. § 112, 2nd Paragraph

In the Office Action, rejections of claims 55, 64, 66 and 81 were maintained under § 112, second paragraph. Without acquiescing in the propriety of any of these rejections, the specification and claims have been amended herein to obviate these rejections.

Specifically, claim 81 was rejected as being indefinite due to the term "practically sufficient" transport rate. Claim 81 has been amended to remove the reference to practically sufficient transport rate across a barrier.

Claim 55 was rejected as being indefinite because the term "two forms of a substance" is defined using "etc." in the specification. Page 14 of the specification has been amended to remove "etc." from the definition of "two forms of a substance."

Claim 64 was rejected as being indefinite due to the term "common large structures." Claim 64 has been canceled.

Claim 66 was rejected as indefinite due to the term "surfactant-like molecule." Claim 66 has been amended to remove the reference to "surfactant-like molecule."

In view of these amendments, Applicants respectfully submit that the present rejections under § 112, second paragraph are moot, and should be reconsidered and withdrawn.

VI. Rejection of Claim 104 Under 35 U.S.C. § 102(b)

Claim 104 was rejected as allegedly being anticipated by Cevc *et al.*, *Biochem. Biophys. Acta* **1368**: 201-215 (1998) ("Cevc").

Without acquiescing in the propriety of the rejection, Applicants have canceled claim 104, without prejudice to pursuit of the claimed subject matter in this or another application. The present § 102(b) rejection is therefore moot and should be withdrawn.

VII. Rejection of Claims 54-103 Under 35 U.S.C. § 103(a)

Claims 54-103 were rejected as allegedly being obvious over Cevc in view of Drejer *et al.*, *Diabetic Med.* **9**: 335-340 (1992) ("Drejer") and further in view of U.S. Patent No. 4,383,993 to Hussain *et al.* ("Hussain"). Applicants respectfully traverse this rejection.

Applicants' independent claims 54 and 100 are directed to methods of *transnasally* administering a pharmaceutical composition including an active ingredient and a carrier. The carrier contains a penetrant that includes a minute fluid droplet surrounded by a coating of at least two substances, which provide particular recited characteristics with respect to solubilization, aggregation and aggregate diameter, and/or elastic deformation energy.

Cevc describes experiments with a *transdermal* composition used to administer insulin. See, *e.g.*, Cevc, page 211, second paragraph. The composition includes soybean phosphatidylcholine and a surfactant such as sodium cholate. Cevc, page 202, last paragraph.

Drejer teaches the nasal administration of insulin with didecanoyl-L-alpha-phosphatidylcholine as an absorption enhancer. Drejer, Abstract.

Hussain discloses a composition for nasal administration of progesterone and 17 β-estradiol, which can be formulated with Tween-80 as a solubilizing agent. Hussain, column 2, lines 10-17; column 3, lines 34-42; column 4, lines 52-56.

Claims 54 and 100 are not *prima facie* obvious over Cevc in view of Drejer and Hussain, at least because the references, even in combination, do not teach or suggest every element of the claimed methods.

Importantly, none of the cited references provides any teaching or suggestion regarding designing a *transnasal* composition that provides the particular claimed characteristics, namely, a penetrant in the form of a minute fluid droplet with a coating of at least *two substances* (*i.e.*, a lipid and a surfactant or more soluble form of the lipid) that differ by at least a factor of 10 in solubility, the substances forming aggregates with specified diameter limitations, the more soluble substance solubilizing the droplet, and/or the coated droplet having a particular elastic deformation energy as claimed. The specific claimed attributes of the penetrant promote the attainment of ultradeformable aspects, which provide for the efficient transfer of the composition across the *transnasal* barrier to effect the claimed methods.

Cevc is directed to carriers for *transdermal* rather than *transnasal* administration. Although Hussain and Drejer disclose transnasal compositions, neither reference provides detail regarding the shape or form of the administered composition, which is important for effective transnasal administration of a pharmaceutical composition as claimed. Moreover, Drejer identifies some difficulty with the disclosed dosage form. Although bioavailability of 8.3%

compared to intravenous injection was obtained for the transnasal formulation, *nasal irritation* was found to *increase* at the higher dose that tended to provide higher bioavailability, and to *increase* with a repeated number of sprayings. Drejer, page 338, column 2, second paragraph; page 339, column 1, third full paragraph; Tables 4-5. In addition, the Declaration of Dr. Gregor Cevc submitted herewith explains that, while it shares a similar headgroup with some of the phospholipids described in the specification, the particular didecanoyl-L-alpha-phosphatidylcholine absorption enhancer disclosed by Drejer is not expected to form a carrier with a penetrant including layers and aggregates with diameter as claimed (and is expected instead to self-assemble into small aggregates in micellar form). Moreover, Dr. Cevc's Declaration explains that the specific combination of the didecanoyl-L-alpha-phosphatidylcholine disclosed by Drejer with the Tween 80 of Hussain would be unlikely to form a penetrant composition having layers and aggregates with diameter as claimed (and instead would likely form micelles).

Thus, even in combination, the cited references do not teach or suggest every limitation of the transnasal methods and carriers recited in claim 54 or 100.

Furthermore, there would be no reason for one of ordinary skill in the art to combine the teachings of Cevc, relating to a *transdermal* formulation, with the teachings of Hussain and Drejer relating to specific transnasal compositions. Cevc does not disclose a *transnasal* carrier, and there is no teaching in Cevc that would motivate one of ordinary skill in the art to use the disclosed composition *transnasally*. To the contrary, Cevc teaches away from *transnasal* administration by expressly indicating that this likely would *not* be a viable approach. The first "chief finding" identified by Cevc is that "*[t]ransepidermal water activity gradient* can push the hydrophilic entities into and across the skin if their resistance to penetration is small enough." Cevc, page 204, second column, last two paragraphs (emphasis added). Thus, Cevc indicates that *transdermal* delivery is made feasible by the presence of a *transepidermal water activity gradient*, which *does <u>not</u> exist* in the *strongly hydrated* nasal mucosal membranes. Put another way, Cevc discloses that the driving force behind the penetration of lipid vesicles across the *skin* is created by a difference in water concentration across the skin, which defines a *hydration force* through which delivery of agents across the skin barrier occurs. The lipid carriers of Cevc are designed for lipid aggregate penetration through the *transdermal barrier* by this hydration force,

wherein "[t]he match of the high membrane deformability and of the good carrier sensitivity to the transepidermal osmotic stress also maximizes the speed of carrier penetration through the skin." Cevc, page 208, column 1, third full paragraph. This hydration force is simply *absent* from the *transnasal* barrier traversed by the claimed *transnasal* compositions, because the nasal/mucosal barrier is in a constant state of humidity/hydration. Accordingly, one of ordinary skill in the art reading Cevc would not reasonably consider applying the disclosed composition nasally.

As discussed in the Declaration of Dr. Gregor Cevc submitted herewith, contrary to the teachings of the Cevc reference, the claimed *transnasal* compositions were *unexpectedly* discovered to provide highly adaptable penetrants that are transported across the nasal mucosa, despite a high water content on *both* sides of this mucosal barrier, in part due to a high humidity concentration associated with exhaled air. In the specification the present inventors, including Dr. Cevc, express their own surprise that the ultradeformable lipid vesicles could be administered nasally:

> The present invention is, in view of the prior art, particularly surprising since ultradeformable lipid vesicles *would seem unsuitable for the purpose of transnasal delivery* taken that they were reported to date to cross barriers, such as skin, only under non-occlusive conditions, that is *in the presence of a strong trans-barrier water concentration gradient* (Cevc *et al.* 1995; Paul and Cevc, 1995), *which is believed <u>not</u> to exist in the strongly hydrated nasal mucosa.*" Specification, page 16, penultimate paragraph (emphasis added).

Thus, Cevc teaches away from nasal administration, such that one of ordinary skill in the art would not have expected to succeed in administering the disclosed carriers transnasally, and would have had no reason to combine the teachings of Cevc with the disclosures of Drejer and Hussain relating to transnasal compositions.

Furthermore, there would be no reason for one of ordinary skill in the art to combine the individual teachings of Drejer and Hussain disclosing different transnasal compositions. Neither Drejer nor Hussain provides any hint that combining formulations containing *both* Tween-80 and

phosphatidylcholine would result in any useful method. The fact that each carrier substance was successful individually does not mean that the two combined would provide a useful carrier. Indeed, Drejer *teaches away* from intranasal administration of a composition containing a lipid and a detergent, such as the Tween 80 disclosed by Hussain. In particular, Drejer provides that "[c]ertain detergents at high concentrations disrupt and even dissolve biological membranes." Drejer, page 339, column 1, fifth paragraph. In contrast, Drejer explains that "the formulation used in the present study caused only slight irritation, probably because the substances used are naturally abundant in humans." Drejer, page 339, column 1, fifth paragraph. Therefore, Drejer teaches away from any combination with Hussain.

Moreover, the Declaration of Dr. Gregor Cevc submitted herewith explains that attempting to use the individual components disclosed by Drejer or Hussain in combination with another lipid component likely would render the disclosed carrier compositions of the references less suitable or unsuitable for their intended purposes, *i.e.*, an absorption enhancer (Drejer) or solubilizing agent (Hussain). In addition, as noted above, Dr. Cevc's Declaration explains that the specific combination of the didecanoyl-L-alpha-phosphatidylcholine disclosed by Drejer with the Tween 80 of Hussain would be unlikely to form a penetrant composition having layers and aggregates with diameter as claimed (and instead would likely form micelles).

Thus, one of ordinary skill in the art would not have any reason to attempt to combine the cited references to achieve the claimed invention, and in any event would be unlikely to succeed and would require undue experimentation to do so. This is particularly true given that Cevc expressly teaches away from any reasonable use of the described compositions for transnasal administration, and Drejer identifies disadvantages of detergents, and of higher doses and repeated transnasal administration of the disclosed compositions. Accordingly, only a hindsight analysis in view of Applicants' own teachings could inspire the asserted combination of references.

In sum, *prima facie* obviousness has not been established, and claims 54 and 100 and their dependent claims are not obvious in view of the cited references alone or in combination. Even if *prima facie* obviousness had been established, it would be overcome by the unexpected ability of the claimed methods to function *transnasally*, despite teachings in the Cevc reference

suggesting the contrary. Thus, Applicants respectfully request that the present rejection under § 103 be reconsidered and withdrawn.

VIII. Conclusion

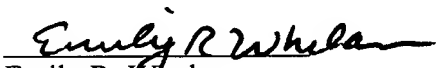
In view of the amendment and arguments set forth above, Applicants respectfully submit that the objections and rejections contained in the Final Office Action mailed on January 29, 2007 have been overcome, and that the pending claims are in condition for allowance.

Applicants hereby petition for a two-month extension of time to respond to the Final Office Action of January 29, 2007. Please deduct the $450.00 fee for this purpose from our Deposit Account No. 08-0219. Please also charge the $790.00 fee for this Request for Continued Examination to our Deposit Account No. 08-0219. No other fees are believed to be due in connection with this correspondence. However, please charge any payments due or credit any overpayments to our Deposit Account No. 08-0219.

The Examiner is encouraged to telephone the undersigned at the number listed below in order to expedite the prosecution of this application.

Respectfully submitted,

Dated: 6/28/07



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